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The Cost-Effectiveness of an Extended Course (12 + 12 Weeks) of Varenicline Compared with Other Available Smoking Cessation Strategies in the United States: An Extension and Update to the BENESCO Model

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ABSTRACT

Objectives: This study aimed to estimate the cost-effectiveness of an extended (12 + 12 weeks) course of varenicline using the (Benefits of Smoking Cessation on Outcomes) BENESCO smoking cessation model.
Methods: Data on the efficacy of 12 + 12 weeks varenicline therapy in aiding smoking cessation were analyzed in conjunction with the efficacy data for 12 weeks of varenicline, bupropion, and placebo previously included in the BENESCO model, by using a mixed treatment comparison. This analysis provided updated efficacy estimates for all the interventions, and these were used to update the model to estimate the relative cost-effectiveness of all smoking cessation interventions considered, now including 12 + 12 weeks of varenicline.
Results: The updated 1-year abstinence estimates derived from the mixed treatment comparison were, for 12 + 12 weeks of varenicline, 12 weeks of varenicline, 12 weeks of bupropion, and 12 weeks of placebo, respectively: 27.7%, 22.9%, 15.9%, and 9.3%. The average cost of the course of 12 + 12 weeks of varenicline was estimated at $603.89, based on a 12-week course followed by a further 12 weeks for successful quitters. Over all subjects' lifetimes, 12 + 12 weeks of varenicline is less costly and more effective than (dominates) all other strategies compared in the updated BENESCO model, with the exception of 12 weeks of varenicline. In this comparison, 12 + 12 weeks of varenicline is a very cost-effective alternative to the 12-week course, with an incremental cost of less than $1000 per quality-adjusted life year (QALY) gained.
Conclusions: A total of 12 weeks of varenicline followed by a further 12-week course for successful quitters is a highly cost-effective alternative compared with currently available smoking cessation options.
Keywords: cost-effectiveness, extended course, maintenance therapy, smoking cessation, varenicline.

Introduction

The consequences of smoking impose a global burden of mortality, morbidity, and cost [1]. Effective smoking cessation has been cited as one of the most cost-effective interventions that are possible within a health-care system because the gains in health outcomes and economic benefits are considerable [2].

A number of smoking cessation alternatives are available, but the most recently approved of these, varenicline, has demonstrated superior levels of smoking cessation efficacy than any existing alternative. Varenicline binds with high affinity and selectivity at the α4β2 neuronal nicotinic acetylcholine receptor, where it acts as a partial agonist, resulting in a reduction in craving for and withdrawal from nicotine.

Compared with placebo, nicotine replacement therapy (NRT) and bupropion SR approximately double the odds of staying abstinent 6 to 12 months after quitting [3,4], whereas varenicline raises the odds of one-year abstinence by 2.5 to 3 times [5–7].

Previous health economic modeling has demonstrated that a 12-week course of varenicline is a highly cost-effective smoking cessation intervention, dominating all other alternatives over the lifetime time horizon [8]. The National Institute for Health and Clinical Excellence has also endorsed the use of varenicline within its licensed indication [9]. New data that support the use of an extended course of varenicline are now available, with a further 12 weeks of treatment in subjects who have successfully quit after an initial 12 weeks of treatment [10]. This analysis models the cost-effectiveness of this extended varenicline treatment course in comparison with all currently available smoking cessation alternatives.

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Patients and Methods

The (Benefits of Smoking Cessation on Outcomes) BENESCO Model

The BENESCO model is a Markov model simulation of the effects of various smoking cessation interventions in a population of adult American smokers and has previously been published [8]. The model is based on the earlier Health and Economic Consequences of Smoking (HECOS) model [11]. The modeled population is the 25% of smokers in the United States who are assumed to make a single quit attempt. The size and demography of this starting population were based on the 2004 census figures [12] and published smoking rates [13] (11.9 million subjects from 47.7 million adult smokers). The model allows a single smoking quit attempt during the first year, and no further attempts may be made. Successful quitters have diminishing chances of relapsing back to smoking each year in the model. Relapse rates are independent of the initial smoking cessation intervention used. The incidence of smoking-related morbidities is modeled, with the diseases considered being lung cancer, stroke, coronary heart disease (CHD), chronic obstructive pulmonary disease (COPD), and asthma. Treatment costs for smoking-related morbidities were drawn from literature [14–18], and smoking cessation intervention costs were based on 2005 US Red Book prices [19]. Utility values for the various model states were also drawn from a variety of literature sources [20–27]. The relative risks between smokers and nonsmokers of incidence and

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mortality from smoking-related morbidities are based on the hazard ratios published by Thun from the Cancer Study (CPS) II Study [28]. Direct costs, quality-adjusted life years (QALYs), and life years are totaled in the model and discounted at 3% per year. Incremental cost-effectiveness ratios (ICERs) in the form of incremental cost per QALY gained and incremental cost per life year gained are calculated over the time frames of 5, 10, and 20 years and the lifetime of the cohort. One-way and probabilistic sensitivity analyses were conducted, with the probabilistic analyses focusing on uncertainty in utility values, morbidity treatment costs, and relative efficacies of the smoking cessation interventions.

Over 20 years, and also over the lifetime of all subjects, 12 weeks of treatment with varenicline was previously found to be less costly and more effective (the dominant strategy) than the other smoking cessation strategies considered in the BENESCO model, namely, bupropion, NRT, placebo, and unaided cessation [8]. Probabilistic and univariate sensitivity analyses appeared to demonstrate that the underlying model was stable and that it was most sensitive to the assumptions around effectiveness estimates (1-year quit rates) and baseline utility values.

The model results were driven by the following underlying behavior. Large numbers of subjects (25% of the smoking population) attempting to quit in the first year cause a large initial treatment cost. Subsequently, the costs and outcomes are driven by the relative effectiveness of the quitting strategy attempted. After the first year, subjects are either smokers (those who relapsed or did not successfully quit) or successful quitters (those who successfully quit and have avoided relapse). Smoking-related morbidities may then occur at higher rates in the smoking population. Consequently, smokers in the model may expect to experience lesser life expectancy and quality of life (because of morbidity and mortality) and incur more costs (because of morbidity) than nonsmokers. Less successful smoking cessation interventions are therefore associated with lower life expectancy, lower quality of life, and higher nontreatment costs.

New Evidence

A randomized, double-blind trial published in 2006 [10] examined the benefits of 12 weeks of maintenance therapy with varenicline (or placebo) in subjects who have successfully quit after 12 weeks of initial open-label varenicline therapy. Subjects were adult smokers (aged between 18 and 75 years) who smoked an average of 10 or more cigarettes a day, who had not had an abstinent period of over 3 months in the previous year, and were motivated to quit.

In an initial, single-arm, open-label phase, 1927 subjects received varenicline for 12 weeks. There were 717 patients who relapsed to smoking by the end of the first 12 weeks. The 1210 subjects who were abstinent entered into the randomized, double-blind maintenance phase. The maintenance phase consisted of 12 further weeks of treatment and follow-up for a further 28 weeks, so that abstinence 52 weeks after initial cessation attempt could be assessed. There were 603 patients randomized to varenicline maintenance and 607 patients randomized to placebo. After the follow-up at the end of the maintenance phase, 263 (43.6%) of the subjects receiving varenicline maintenance therapy were confirmed abstinent, compared with 224 (36.9%) of those receiving placebo maintenance.

Updating the BENESCO Model

The BENESCO model was updated to include the 12 + 12 weeks of varenicline as a further treatment option. The 12 + 12 weeks was composed of 12 weeks of initial therapy with 1 mg varenicline twice daily followed by 12 weeks of maintenance therapy, again 1 mg twice daily. The maintenance therapy was only provided to those subjects who were successfully abstinent after the initial 12 weeks of varenicline. This treatment strategy matched the design of the new trial [10].

The data from the 12 + 12-week varenicline study [10] were combined with the various efficacy data used to inform the original BENESCO model, within a mixed treatment comparison [29]. This technique allows data from many studies with various shared comparators to be combined to provide estimates of comparative effect. These estimates were then used as the new efficacy figures to drive the BENESCO model.

The cost of the 12 + 12-week course of varenicline was also calculated and added into the updated model. All subjects starting a 12 + 12-week course of varenicline incur 12 weeks of costs (covering one physician visit and 12 weeks of varenicline). Based on the reported 12-week abstinence rates [10], 63% of subjects will then commence a further 12 weeks of maintenance therapy (another physician visit and a further 12 weeks of varenicline). The cost of the 12 + 12-week course was therefore calculated as two times the cost of the 12-week course for 63% of subjects and one times the cost for the remainder.

Patient Population

The population modeled in the BENESCO model is based on the 2004 census figures for the United States [12]. Subjects included are aged 18 or above and are split into age bands (18–34, 35–64, and 65+) and by sex.

Smoking prevalence rates are taken from the 2005 National Health Interview Survey report [13] and calculated for the age and sex groupings.

The model assumes that 25% of all adult smokers will make a quit attempt and that the attempt occurs at the start of the model, so that the 1-year quit rates apply during the first year of the model.

Efficacy Update Methodology

The smoking cessation strategies included as options within the BENESCO model are varenicline, bupropion, NRT, and unaided cessation.

The quit rates for each treatment other than NRT were estimated by using mixed treatment comparison methods [29]. An advantage of this approach is that efficacy parameters for placebo, bupropion, and varenicline treatments could be estimated simultaneously from the randomized controlled trial (RCT) data by using one internally consistent statistical model. For treatments $j = 1, \ldots, J$ assessed in trials $i = 1, \ldots, I$, the number of patients who quit n_{ij} is assumed to follow a binomial distribution according to the number of patients randomized to that treatment arm N_{ij} and a probability parameter π_{ij} (Equation 1):

$$n_{ij} \sim Bi(N_{ij}, \pi_{ij}) \tag{1}$$

The quit log odds is modeled as the sum of a study random effect μ_i and a study and treatment specific random effect δ_{ij}, which may be interpreted as a log odds ratio for treatment j in study i (Equation 2).

$$\log\left(\frac{\pi_{ij}}{1-\pi_{ij}}\right) = \mu_i + \delta_{ij} \tag{2}$$

The study and treatment effect are assumed to arise from a normal distribution with mean $\bar{\delta}_j$. Here, we have data from three trials ($I = 3$) and four treatments ($J = 4$), as shown in Table 1. We

Table 1 Proportions and numbers of patients who had quit at 12 months

Reference	Placebo (%)	Varenicline (12 weeks) (%)	Varenicline (12 + 12 weeks) (%)	Bupropion (12 weeks) (%)
Tonstad [10]*	—	23.2 (N = 603)	27.4 (N = 607)	—
Jorenby [7]	10.3 (35 out of 341)	23.0 (79 out of 344)	—	14.6 (50 out of 342)
Gonzalez [5]	8.4 (29 out of 344)	21.9 (77 out of 352)	—	16.1 (53 out of 329)

*The sample sizes given for Tonstad et al. refer to the 1210 patients from this trial of 1927 patients whose smoking had not relapsed by the end of 12 weeks.

set $\delta_{i,1} = 0$ for the identification of all the parameters. The quit rates for each treatment j are then estimated as $\bar{\mu} + \bar{\delta}_j$ where $\bar{\mu}$ is the average study effect for studies with placebo arms.

The study providing efficacy evidence for varenicline given over 12 + 12 weeks was the two-stage study described earlier [10]. The 52-week efficacy of 12 weeks treatment with varenicline from this study was calculated as the product of the efficacy from the first 12 weeks varenicline treatment and the efficacy from the follow-up to 1 year of a subsequent 12 weeks of placebo treatment: 23.2% (=1210 out of 1927 × 224 out of 607). The 52-week efficacy of 12 + 12 week varenicline was calculated as the product of the efficacy from the first 12 weeks varenicline treatment and the efficacy from the follow-up to 1 year of the subsequent 12 weeks of varenicline treatment: 27.4% (=1210 out of 1927 × 263 out of 603). For the purposes of the mixed treatment comparison and so as not to overweight this study, these efficacy data were assumed to arise from 603 and 607 patients.

Results

Efficacy Summary

The data used to drive the mixed treatment comparison of varenicline, bupropion, and placebo are shown in Table 1. The calculated 1-year quit rates for 12 weeks of varenicline and bupropion are higher than the values used in the original BENESCO model (22.9% vs. 22.4% for 12 weeks varenicline, 15.9% vs. 15.4% for 12 weeks bupropion). The changes in these values are due to both the change in calculation method (mixed treatment comparison compared with simple pooling of numbers) as well as the inclusion of additional data on 12 weeks of varenicline efficacy from the extra included study.

The resulting updated 1-year quit rates used in the updated BENESCO model, along with the pooled figures used in the initial version of the model for comparison, are shown in Table 2.

The derivation of the efficacy rate for NRT is unchanged from the methodology used in the original BENESCO model: it is calculated by using a published odds ratio from a meta-analysis by Silagy et al. [3]. This figure (odds ratio 1.77, 95% confidence interval: 1.66, 1.88, $P < 0.00001$) is combined with the 1-year quit rate estimated above for placebo to derive an estimate of the 1-year quit rate for NRT. The resulting estimate for NRT efficacy is shown in Table 2.

Table 2 Efficacy assumptions (1-year quit rate) and costs of various treatment courses used in the updated BENESCO model

Treatment	% Abstinent at 1 year	Previous value used in original BENESCO model (% abstinent at 1 year)	Cost of intervention (US$)
Unaided cessation	5.0	5.0	0
Placebo	9.3	9.3	0
NRT	15.4	15.4	405.47
Bupropion	15.9	15.4	264.40
Varenicline (12 weeks)	22.9	22.4	370.96
Varenicline (12 + 12 weeks)	27.7	—	603.89

BENESCO, Benefits of Smoking Cessation on Outcomes; NRT, nicotine replacement therapy.

Costs Summary

The costs of the smoking cessation interventions are unchanged from the values calculated and used in the original model. These are reproduced in Table 2, alongside the average cost per quit attempt for 12 + 12 weeks of varenicline, the new intervention included in the model.

Summary Results

There are two sources of change to the results of the BENESCO model. Firstly, the new treatment comparator (12 + 12 weeks of varenicline) extends the tables of results by treatment. Secondly, the updated efficacy figures, now derived from the mixed treatment comparison, causes all the results to change slightly from their previously published values. General patterns and overall conclusions regarding cost-effectiveness and time frames to dominance are not changed.

Tables 3 and 4 show the summary results for the 12- and 12 + 12-week courses of varenicline as well as the 12-week course of bupropion, NRT, and unaided cessation. Only the varenicline (12 weeks) and bupropion per-treatment results are different from those published in the original report [8], but results for NRT and unaided cessation are presented again for ease of comparison.

Summary ICERs

The incremental cost-effectiveness ratios estimated by the updated BENESCO model are presented in Table 5. Over the lifetime of all subjects in the model, 12 + 12 weeks of varenicline is less costly and more effective than (dominates) all other strategies compared in the updated BENESCO model, with the exception of 12 weeks of varenicline. In the case of this comparison, 12 + 12 weeks of varenicline is a very cost-effective alternative to the 12-week course, with an incremental cost of less than $1000 per QALY gained.

Updated Probabilistic Sensitivity Analysis

As part of the update to the BENESCO model, the probabilistic sensitivity analysis as defined in the original model [8] was extended to include 12 + 12 weeks of varenicline. A summary of the results from 500-run simultaneous comparisons of 12 + 12 weeks of varenicline with the other smoking cessation treatments included in the updated BENESCO model is presented in Table 6, and the findings are consistent with those from the original BENESCO model. The results suggest that the model is stable, and 12 + 12 weeks of varenicline is acceptably cost-effective (using a threshold of $30,000 per QALY gained) in at least 70% of probabilistic runs, regardless of the comparator treatment.

Discussion

The findings of this extension to the BENESCO model are in keeping with the findings of the original publication, namely, that

Table 3 Cumulative mortality estimated from the updated BENESCO model

Model year	Lifetime
Varenicline (12 + 12 weeks)	
COPD	487,696
Lung cancer	1,568,223
CHD	659,616
Stroke	417,189
Subtotal	3,132,725
Other cause	8,792,730
Total	11,925,455
Varenicline (12 weeks)	
COPD	494,334
Lung cancer	1,592,214
CHD	665,133
Stroke	420,758
Subtotal	3,172,439
Other cause	8,753,016
Total	11,925,455
Bupropion	
COPD	504,001
Lung cancer	1,627,151
CHD	673,166
Stroke	425,956
Subtotal	3,230,274
Other cause	8,695,181
Total	11,925,455
NRT	
COPD	504,665
Lung cancer	1,629,550
CHD	673,718
Stroke	426,313
Subtotal	3,234,245
Other cause	8,691,210
Total	11,925,455
Unaided cessation	
COPD	519,090
Lung cancer	1,681,680
CHD	685,704
Stroke	434,068
Subtotal	3,320,542
Other cause	8,604,913
Total	11,925,455

BENESCO, Benefits of Smoking Cessation on Outcomes; CHD, coronary heart disease; COPD, chronic obstructive pulmonary disease; NRT, nicotine replacement therapy.

Table 4 Cumulative incidence of smoking-related morbidities and cumulative direct health costs (million US dollars) estimated from the updated BENESCO model, after discounting at 3% a year

Model year	Lifetime cumulative incidence of smoking-related morbidities	Lifetime cumulative direct health costs (million US dollars)
Varenicline (12 + 12 weeks)		
COPD	969,179	64,016
Lung cancer	1,702,248	48,884
CHD	1,296,450	65,882
Stroke	882,886	140,664
Asthma exacerbations	1,834,158	1,881
Total	4,850,762	321,326
Varenicline (12 weeks)		
COPD	995,352	64,539
Lung cancer	1,728,442	49,731
CHD	1,308,544	66,171
Stroke	889,792	141,528
Asthma exacerbations	1,834,854	1,885
Total	4,922,130	323,855
Bupropion		
COPD	1,033,467	65,302
Lung cancer	1,766,587	50,964
CHD	1,326,157	66,592
Stroke	899,848	142,787
Asthma exacerbations	1,835,867	1,892
Total	5,026,059	327,537
NRT		
COPD	1,036,084	65,354
Lung cancer	1,769,207	51,048
CHD	1,327,366	66,621
Stroke	900,539	142,874
Asthma exacerbations	1,835,936	1,892
Total	5,033,196	327,789
Unaided cessation		
COPD	1,092,957	66,492
Lung cancer	1,826,125	52,888
CHD	1,353,646	67,249
Stroke	915,544	144,752
Asthma exacerbations	1,837,448	1,902
Total	5,188,273	333,283

CHD, coronary heart disease; COPD, chronic obstructive pulmonary disease.

Table 5 Incremental cost per QALY analysis calculated from the updated BENESCO model over the lifetime of all subjects, after discounting of 3% a year

Intervention	Cost (Millions, US $)	QALYs (1000s)	Incremental costs (Millions, US$)	Incremental QALYs (1000s)	ICER
Varenicline (12 weeks)	328,279	174,373			
Varenicline (12 + 12 weeks)	328,528	174,630	249	257	$972
Bupropion	330,689	173,999	2,161	–631	Dominated
NRT	332,622	173,970	1,933	–29	Dominated
Unaided cessation	333,283	173,416	661	–554	Dominated

ICER, incremental cost-effectiveness ratio; NRT, nicotine replacement therapy; QALY, quality-adjusted life years.

Table 6 Probability of being cost-effective at various willingness to pay thresholds for 1 QALY, from the updated BENESCO model

	Willingness to pay for 1 QALY (%)					
Intervention	$0	$10,000	$20,000	$30,000	$40,000	$50,000
Varenicline (12 + 12 weeks)	41	67	71	73	73	73
Varenicline (12 weeks)	59	19	11	9	8	7
Bupropion	0	0	0	0	0	0
NRT	0	0	0	0	0	0
Unaided cessation	0	14	18	19	19	19

Columns may not add to 100% due to rounding.
NRT, nicotine replacement therapy; QALY, quality-adjusted life years.

the higher purchase cost of varenicline is more than outweighed over patients' lifetimes by the benefits gained from its higher efficacy in terms of 1-year quit rate, and the subsequent benefits in terms of smoking-related morbidity and mortality for subjects who successfully quit smoking. This pattern of long-term cost-effectiveness is further demonstrated by the 12 + 12-week course of varenicline, compared with all other smoking cessation strategies included in our model.

The difference between the 12 + 12 and 12-week varenicline strategies is reflected in the BENESCO model inputs through a difference in the first year efficacy (27.4% vs. 23.2%) and treatment costs ($603.89 vs. $370.96). The increased efficacy leads to a higher proportion of subjects successfully quitting smoking at the start of the model, leading to decreased risks of modeled comorbidities throughout the subjects' lifetimes, provided that they do not relapse to smoking. The BENESCO model shows that the long-term benefits of smoking cessation, in the form of decreased risks of contracting life-threatening and life-affecting costly comorbidities, more than offset the short-term, one-off costs of the pharmacotherapy itself. A 12 + 12-week course of varenicline increases the chance of initial success at an acceptable initial extra cost over a 12-week course of varenicline.

One criticism that could have been leveled at the original BENESCO model was regarding the pooling of the efficacy data for varenicline, bupropion, and placebo: this may be regarded as a slightly simplistic approach. This updated version of the model now uses a mixed treatment comparison, based on the methodology published by Ades et al. [29], and this should be considered as a more robust method of combining various treatment comparison data simultaneously in a consistent manner. The efficacy inputs for placebo, bupropion, varenicline 12, and varenicline 12 + 12 are estimated from the available clinical trial data simultaneously by using one internally consistent statistical model.

The efficacy data for the various treatment strategies from the original BENESCO model [8] may well be out of date now, with other studies and publications doubtless adding to the evidence pool. The authors acknowledge that a full update to the BENESCO model, updating all input data in line with analysis of the latest available information, including updated meta-analyses of all efficacy figures, would give valuable further insight in this area. This was not, however, the purpose of this particular update analysis.

As noted in the original BENESCO model discussions, the perspective of the model is limited to direct treatment costs for the interventions and the smoking-related morbidities considered in the model. As such, other treatment and nontreatment (non-direct) costs are not considered in the model, and this is a standard issue with long-term smoking cessation models. This perspective adopted by the model will therefore ignore many of the wider economic impacts of smoking-related diseases, including lost productivity because of ill health and early mortality, and this exclusion biases the model against the fuller economic benefits of smoking cessation.

Discount rates for costs, QALYs, and life years are set at 3%, in line with the original BENESCO model. It is recommended by Gold et al. [30], among others, that the same rates be used for discounting costs and benefits (life years and QALYs) although others state the case for differential discounting. There is additionally some debate as to the best value to set these figures at. We feel that Gold's recommendation of 3% for the base case is still suitable for this model and it is very close to the National Institute of Health and Clinical Excellence's own recommendation of 3.5% [31].

An additional 12 weeks of varenicline therapy to an initial successful 12 weeks of varenicline therapy is estimated to lead to an increase in 1-year abstinence, from 22.9% to 27.7%, of subjects who attempt to quit. This additional benefit is considered acceptably cost-effective in comparison with a 12-week course of varenicline, with the incremental cost-effectiveness ratio being $972, far below a threshold of $30,000 per QALY gained. We have not estimated a confidence interval for this ratio, which may be considered a limitation of our calculations, but we note, as mentioned earlier, that over 70% of the probabilistic sensitivity analysis simulations were at or below a willingness-to-pay threshold of $30,000 per QALY, and further analysis estimates that over 60% of simulations are at or below a threshold of $5000, suggesting that the conclusion of incremental cost-effectiveness is quite robust.

The ability of the BENESCO model to allow the incorporation of additional treatment comparisons and updated clinical trial data, without radical changes in the results and conclusions, shows the flexibility and versatility of the underlying model structure.

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